Molecular insights into the germline for prostate cancer initiation, progression, and aggressiveness

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Germline and tumor genetic testing of DNA repair genes in men with advanced prostate is increasingly recommended by U.S. and international guidelines as part of standard of care. Damaging mutations in homologous DNA repair pathways genes including BRCA2, BRCA1, PALB2, and ATM, and mismatch DNA repair genes including MSH2 and MSH6 have emerging clinical utility for risk assessment and treatment decision-making. This article summarizes a presentation at the 2019 Philadelphia Consensus Conference focused on the latest data at the intersection of germline and tumor genetic testing for prostate cancer patients.

Key Words: *BRCA1, BRCA2, ATM, MSH2, MSI,* genetic testing

Introduction

Multiple large studies in the past 3 years have revealed a higher-than-expected prevalence of autosomal dominant high and moderate penetrance germline DNA gene mutations in men with advanced prostate cancer.[1-5] At the same time, there is increasing evidence that loss-of-function mutations in DNA repair genes are highly predictive of treatment responses. This work has led to the rapid adoption of both germline and somatic (tumor) panel testing for DNA repair genes in men with advanced prostate cancer. The emerging model for care of men with advanced prostate cancer involves genetic testing to guide therapy, risk assessment, and risk counseling.

Materials and methods

Literature review was performed of recent large prostate cancer studies into germline and somatic DNA repair gene mutation prevalence estimates, clinical utility for treatment, and tumor features that may help providers identify potential germline carriers. Review was mostly limited to DNA repair genes in the homologous recombination (HR) and mismatch repair (MMR) pathways in which there are well-known risk syndromes.

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The overall prevalence of germline pathogenic and likely pathogenic mutations in *BRCA2*, *BRCA1*, *PALB2*, *ATM* (HR) and *MSH2*, and *MSH6* (MMR) among five large studies is summarized in Table 1. There are many additional genes that have been evaluated in prostate cancer in these pathways. These six genes were selected because they are among the best-studied with regard to prostate cancer risk and treatment decision making. Among HR pathway genes *BRCA2* is the most commonly mutated in the germline and among MMR, *MSH2* is most common.

Features of prostate cancer patients harboring damaging germline mutations in key HR and MMR genes are listed in Table 2, including relative prostate cancer risk, expected family history and other cancer risks, tumor features that are characteristic in patients harboring mutations for each specific gene, and level of evidence of treatment responses. For most of the HR and MMR genes there are not yet well-characterized lifetime prostate cancer risk estimates. Risk of other cancers are well-defined for many of these genes and can provide clues from the family history.

Tumor features are associated with specific germline pathogenic variants but are not specific. For patients harboring germline HR DNA repair mutations, particularly in *BRCA2*, the presence of intraductal or ductal histology is often present.[6-7] Newer assays are becoming available to assess a "BRCAness" mutational signature in prostate tumors but are not yet standard-

TABLE 1. **Germline mutation prevalence in selected DNA repair genes in advanced prostate cancer**

	Pritchard 2016[1]	Na 2017[5]	Annala 2017[4]	Giri 2019[3]*	Nicolosi 2019[2]*	Combined
N	692	313	319	1328	3,607	6259
BRCA2	5.3%	3.5%	5.0%	4.5%	4.7%	4.7%
BRCA1	0.9%	0.6%	0.3%	1.1%	1.3%	1.1%
PALB2	0.4%	NA	0.6%	0.5%	0.6%	0.5%
ATM	1.6%	1.9%	0.3%	1.8%	2.0%	1.8%
MSH2	0.1%	NA	0.0%	0.5%	0.7%	0.5%
MSH6	0.1%	NA	0.0%	0.4%	0.5%	0.4%

*these studies included some patients with localized disease

of-care. These assays will assist in the future in helping to determine whether a germline pathogenic mutation in an HR gene is a driver of the cancer. Particularly for moderate to low penetrance genes such as *ATM* or *CHEK2* one cannot assume that a prostate cancer is driven by an underling germline pathogenic mutation.

For prostate cancer patients harboring germline MMR DNA repair mutations (Lynch syndrome patients), tumors will often have microsatellite instability (MSI). MSI is the genomic hallmark of MMR deficiency (MMRd) and a reliable way to determine if the underlying germline MMR mutation was part of tumorigeneses. However, many MSI assays have not been well-validated for prostate cancer so the sensitivity is not optimal. Another tumor clue to MMRd is elevated total mutation burden (TMB), a test increasingly performed as part of a next-generation sequencing large panel tumor assessment. Histologic clues that point to

TABLE 2. **Features of DNA repair genes commonly tested in men with prostate cancer**

Gene	Pathway	Prostate cancer risk	Other family history	Tumor features	PARP/ platinum response	Anti PD1/ PDL1 response
BRCA2	HR	High	Br, Ov, Panc	Intraductal/ductal	+++++	
BRCA1	HR	Moderate	Br, Ov	Intraductal/ductal	++++	
PALB2	HR	Mod/high	Br, Ov, Panc	Intraductal/ductal	+++	
ATM	HR	Moderate	Br, Ov	Intraductal/ductal	++	
CHEK2	HR	Moderate	Br, Ov, CRC	Emerging	+	
NBN	HR	Some data	Br	Emerging	+/-	
RAD51C	HR	Emerging	Ov	Emerging	+/-	
RAD51D	HR	Emerging	Ov	Emerging	+/-	
BRIP1	HR	Emerging	Ov	Emerging	+/-	
FANCA	HR	Unknown	?	Emerging	+/-	
MSH2	MMR	High	CRC, endo	MSI, Gl. 5, ductal, ↑TMB		+++++++
MSH6	MMR	Moderate	CRC, endo	MSI, Gl. 5, ductal, ↑TMB		+++++
MLH1	MMR	Moderate	CRC, endo	MSI, Gl. 5, ductal, ↑TMB		++++
PMS2	MMR	Some data	CRC, endo	MSI, Gl. 5, ductal, ↑TMB		+

HR = homologous recombination DNA repair; MMR = mismatch DNA repair; Br = breast cancer; Ov = ovarian cancer; Panc = pancreatic cancer; CRC = colorectal cancer; endo = endometrial cancer; intraductal/ductal refer to rare histologic subtypes; Gl. = primary Gleason grade; MSI = microsatellite instability; TMB = total mutation burden

Lynch syndrome include very high histologic grade (primary Gleason pattern 5) and ductal histology.[7-8] In prostate cancer patients with primary Gleason pattern 5 about 8% had either germline or somatic mutations in *MSH2*, and in patients with ductal histology about 20% had a germline or somatic mutation in a key MMR gene.

There is now good evidence that advanced prostate cancer patients harboring *BRCA2* and *BRCA1* HR DNA repair mutations response to treatments with poly (ADP) ribose polymerase (PARP) inhibitors as well as platinum-based chemotherapy. Evidence for PARPi/platinum responses is emerging for other HR DNA repair genes, Table 2. Similarly, there is strong evidence that MMRd results in favorable response to checkpoint blockade immunotherapy, with pembrolizumab being approved for all tumors (including prostate cancer) with evidence of MMRd. It is worth restating that prostate cancer patients with Lynch syndrome may not have MMRd in their tumors. This is particularly true for patients with germline PMS2 or MLH1 mutations.

In summary, the past few years have been exciting time for genetic testing in prostate cancer as evidence is emerging quickly for clinical utility in risk assessment and treatment decisions.

Disclosures

Dr. Colin C. Pritchard is a consultant for Promega. □

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